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Objectively Measured Secondhand Smoke Exposure and Risk of Cardiovascular Disease

What Is the Mediating Role of Inflammatory and Hemostatic Factors?

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Objectives The aim of this study was to examine the association between objectively measured secondhand smoke (SHS) exposure and incident cardiovascular disease (CVD) death and assess the extent to which this association can be explained through novel circulating markers of inflammation and hemostasis.

Background Existing evidence suggests there is an association between SHS and CVD risk, although the mechanisms remain poorly understood.

Methods In a prospective study of 13,443 participants living in England and Scotland (age 53.5 ± 12.6 years, 52.3% women), we measured salivary cotinine (an objective marker of SHS exposure) and novel CVD biomarkers (C-reactive protein, fibrinogen) at baseline.

Results Of the sample, 20.8% had high SHS exposure on the basis of elevated levels of salivary cotinine (range 0.71 to 14.99 ng/ml). During a mean follow-up of 8 years, there were 1,221 all-cause deaths and 364 CVD deaths. High SHS was associated with all-cause (age-adjusted hazard ratio [HR]: 1.25, 95% confidence interval [CI]: 1.02 to 1.53) and CVD death (age-adjusted HR: 1.21, 95% CI: 0.85 to 1.73). High SHS was also associated with elevated CRP, which explained 48% of the association between SHS and CVD death. The excess risk of CVD associated with active smoking was exaggerated in relation to self report (age-adjusted HR: 3.27, 95% CI: 2.48 to 4.31) compared with objective assessment (age-adjusted HR: 2.44, 95% CI: 1.75 to 3.40).

Conclusions Among a large representative sample of British adults we observed elevated levels of low-grade inflammation in otherwise healthy participants exposed to high SHS, and this partly explained their elevated risk of CVD death. (J Am Coll Cardiol 2010;56:18–23) © 2010 by the American College of Cardiology Foundation

Recent studies that have used valid objective biochemical markers of secondhand smoke (SHS) exposure have found associations with various cardiovascular disease (CVD) risk factors, including socioeconomic deprivation, markers of inflammation, endothelial dysfunction, lipids, and glucose control (1–4). To our knowledge, there are only 2 studies to date that have examined CVD mortality risk with objectively measured biomarkers of SHS exposure (4,5), although 1 of these studies (5) used carboxyhemoglobin concentration that is not a useful indicator of SHS.

Mechanisms explaining the association between SHS exposure and coronary heart disease risk have not been well-examined. The suggestion that the association between SHS and CHD is not markedly attenuated by adjustment for conventional CVD risk factors, such as blood pressure, blood lipids, body mass index, and fasting glucose, raises the possibility that other, novel explanatory factors might be involved. The importance of low-grade inflammation in the link between active smoking and CVD risk is increasingly recognized (6,7), but we are not aware of any existing study that has directly assessed the role of inflammatory and hemostatic markers in relation to SHS exposure.

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In the present study, we examined the association between objectively measured SHS and incident CVD death and assessed the extent to which this association could be explained through 2 circulating markers of inflammation and hemostasis: C-reactive protein (CRP) (8) and fibrinogen (9). We employed salivary cotinine as an objective indicator of nicotine exposure that is considered to be the gold standard measure (10).

Methods

Study design and participants. The Health Survey for England and Scottish Health Survey are annual, ongoing, repeated, cross-sectional, general population-based studies examining individuals living in households in each country (11,12). In the present sample we amalgamated data from both the Scottish Health Survey (1998, 2003) and Health Survey for England (1998, 1999, 2003, 2004). Consenting study members (94% in Health Surveys for England, 82.5% in Scottish Health Surveys) were linked to National Health Service mortality data. The final analytic sample consisted of 13,443 men and women over 35 years of age and free of CVD or cancer (for sample selection, see the Online Appendix). Study participants gave full informed consent and ethical approval was obtained from the London Research Ethics Council.

Assessment of direct and SHS exposure. Data on self-reported smoking were collected with standard methods (11,12) and classified into 3 groups (current/ex-smoker/never). Exposure to SHS was assessed with salivary cotinine, which is a reliable and valid circulating biochemical marker of nicotine exposure (10). A dental roll saturated with participants' saliva was placed in a tube and later analyzed with a Hewlett Packard hp5890 gas chromatograph (Palo Alto, California), with a rapid-liquid chromatography technique (coefficient of variation [CV] <7%). Participants reporting nonsmoking status but with salivary cotinine >15 ng/ml were re-categorized as smokers, in keeping with other analyses (1,4).

Demographic and clinical variables. Computer-assisted personal interviewing modules assessed respondents' demographic data, mental health status, history of disease, and health behaviors. In a separate visit, qualified nurses collected blood samples and measured seated blood pressure. Blood samples were analyzed for CRP, fibrinogen, and total and high-density lipoprotein (HDL) cholesterol. The analysis of CRP levels from serum was performed with the N Latex high-sensitivity CRP mono immunoassay on the Behring Nephelometer II analyzer (Dade Behring, Marburg, Germany) (CV <6%). Fibrinogen levels were determined with the Organon Teknika MDA 180 analyzer (Organon, Teknika, Durham, North Carolina), with a modification of the Clauss thrombin clotting method (CV <10%). Cholesterol and HDL cholesterol was measured with cholesterol oxidase assays on an Olympus 640 analyzer (Olympus, Center Valley, Pennsylvania).

Mortality follow-up. Diagnoses for primary cause of death was recorded with the International Classification of Diseases-9th (ICD-9) and -10th Revisions (ICD-10) Revisions. Cardiovascular disease codes were 390-459 for ICD-9 and I01-I99 for ICD-10.

Statistical analysis. Exposure to nicotine was categorized into 4 groups, representing "low" SHS (salivary cotinine ≤0.05 ng/ml), "moderate" SHS (0.06 to 0.70 ng/ml), "high" SHS (0.71 to 14.99 ng/ml), and "current smoker" (on the basis of self report or cotinine ≥15 ng/ml). This categorization of SHS was based on previous evidence for health effects at this level of exposure (1,4). We used general linear models to examine the association between SHS and biological risk factors. The CRP data were log transformed to normalize the distribution. We used Cox proportional hazards models to compute hazard ratios (HRs) with accompanying 95% confidence intervals (CIs) for the association between cotinine levels and CVD death/all-cause death. The proportional hazards assumption was examined by comparing the cumulative hazard plots grouped on exposure, although no appreciable violations were noted. In these analyses, calendar time (months) was the time scale. For participants that remained alive, the data were censored on February 28, 2008, in the Health Survey for England and December 30, 2008, in the Scottish Health Survey. There were no clear differences in our results between men and women, so the data were pooled and sex-adjusted. We fitted several mutually exclusive models, and the percentage change in HR after multiple adjustments in comparison with the basic (age-adjusted) model was quantified as follows: $(HR_{basic\ model} - HR_{adjusted})/(HR_{basic\ model} - 1) \times 100$ (13). The "nonsmoking" group consisted of both never and ex-smokers, although we conducted sensitivity analyses to examine associations among both groups separately. Statistical significance of $p < 0.05$ was employed throughout. All analyses were conducted with SPSS version 14 (SPSS Inc., Chicago, Illinois).

Abbreviations and Acronyms

- **CI** = confidence interval
- **CRP** = C-reactive protein
- **CV** = coefficient of variation
- **CVD** = cardiovascular disease
- **HDL** = high-density lipoprotein
- **SHS** = secondhand smoke

Results

Characteristics. In the present sample, 28.7% of participants were classified as smokers and 20.8% had high SHS exposure on the basis of levels of salivary cotinine. There was a dose-response relationship between self-reported smoking and cotinine values (Fig. 1). Never smokers and ex-smokers did not differ significantly in levels of salivary cotinine. In comparison with those with lower SHS exposure, both smokers and participants with high SHS were younger, more likely to be male, come from lower social-status groups, live in Scotland, and be less physically active

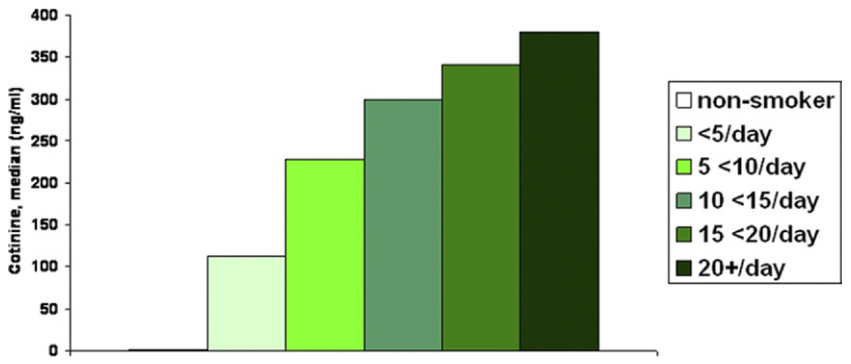

Figure 1 Median Salivary Cotinine Levels in Relation to Self-Reported Smoking Status

There was a dose-response relationship between self-reported smoking (cigarettes/day) and cotinine values. Never smokers and ex-smokers did not differ significantly in levels of salivary cotinine.

(Table 1). Levels of psychological distress were significantly elevated in smokers. Self-reported diabetes was not associated with smoking and only marginally associated with SHS exposure.

Correlations with inflammatory markers. Cigarette smoking was related to increased levels of fibrinogen, CRP, and lower HDL cholesterol (Table 2). High SHS was associated with elevated CRP and blood pressure compared with low SHS. There were also significant associations of CRP and fibrinogen with age, female sex (for fibrinogen), lower physical activity, and low social status/survey location (Online Table A1).

Cotinine and risk of CVD and all-cause death. Over an average follow-up period of 8.0 years (range 1 to 128 months) there were 1,221 all-cause deaths and 364 CVD deaths. As anticipated, conventional risk factors were associated with CVD death (Online Table B1). In the total cohort, the association between SHS category and CVD did not reach conventional levels of statistical significance, although log cotinine as a continuous variable was associated with CVD (per-unit increase; HR: 1.21, 95% CI: 1.15 to 1.25) (Table 3). When we restricted analyses to never-smokers, high SHS exposure was associated with over a 2-fold increased risk of CVD death (Table 3), although there was no association in ex-smokers (HR: 0.87, 95% CI: 0.55 to 1.36). On the basis of self-report, ex-smokers were at elevated risk of CVD compared with never smokers (HR: 1.38, 95% CI: 1.07 to 1.78).

In the total cohort there was a significant association between SHS exposure and all-cause mortality (Table 4). We observed stronger associations in never-smokers (HR: 1.33, 95% CI: 0.94 to 1.88) than in ex-smokers (HR: 1.14, 95% CI: 0.89 to 1.48) although not reaching conventional levels of statistical significance. The removal of 56 deaths within the first 2 years of follow-up did not substantially alter these results.

Proportion of cotinine–CVD association explained by inflammatory markers. When we included all biological risk factors in the models for the total sample, the HR for high SHS and CVD death was attenuated by 48% (Table 3) and by 40% in the case of all-cause mortality (Table 4). This effect was almost entirely explained by CRP, because removal of other risk factors did not impact the result. When behavioral and psychosocial covariates (in addition to biological variables) were included in a fully adjusted model, the point estimate was attenuated to the null. In the case of

Table 1 Baseline Characteristics of the Study Participants According to Nicotine Exposure

	Nonsmoker (Cotinine Level, ng/ml)					
	<0.06 (n = 1,703)	0.06–0.70 (n = 5,089)	0.71–14.99 (n = 2,793)	Smoker (n = 3,859)	p Value for Trend*	p Value for Trend†
Age (yrs)	55.6 ± 13.5	54.2 ± 12.9	53.7 ± 12.5	50.8 ± 11.4	<0.001	<0.001
Sex (men)	41.0	44.0	52.7	51.7	<0.001	<0.001
Lower social status (IV/V)	12.4	14.1	20.3	27.8	<0.001	<0.001
Nationality (Scottish)	49.3	55.0	57.6	61.0	<0.001	<0.001
Psychological distress	11.5	12.1	13.4	18.6	0.125	<0.001
Weekly MVPA (none)	50.6	48.5	55.1	63.3	<0.001	<0.001
Doctor-diagnosed diabetes	2.9	2.4	3.3	2.3	0.06	0.52

N = 13,443. Data given as mean ± SD or percentages. *Trend across nonsmokers; †trend across whole sample.
IV/V = part skilled/unskilled; MVPA = moderate–vigorous physical activity.

Table 2 Association Among SHS Exposure, Smoking, and CVD Risk Markers at Baseline

Exposure (Cotinine Level)	Fibrinogen β (95% CI)	Log CRP β (95% CI)	Systolic BP β (95% CI)	HDL-C β (95% CI)
Low SHS (<0.06 ng/ml)	0 (Reference)	Reference	Reference	Reference
Medium SHS (0.06–0.70 ng/ml)	−0.01 (−0.04 to 0.03)	0.002 (−0.04 to 0.04)	−0.20 (−1.14 to 0.73)	0.002 (−0.03 to 0.03)
High SHS (0.71–14.99 ng/ml)	−0.01 (−0.03 to 0.04)	0.08 (0.04 to 0.13)	1.30 (0.26 to 2.33)	0.006 (−0.02 to 0.03)
Smokers (≥15.00 ng/ml)	0.30 (0.26 to 0.34)	0.28 (0.24 to 0.32)	−0.22 (−1.20 to 0.76)	−0.08 (−0.10 to 0.05)
p value for trend	<0.001	<0.001	<0.001	<0.001

N = 13,443. Models adjusted for age and sex. β-coefficients represent mean differences compared with reference group.
BP = blood pressure; CI = confidence interval; CRP = C-reactive protein; CVD = cardiovascular disease; HDL-C = high-density lipoprotein cholesterol; SHS = secondhand smoke.

smoking, however, there remained an elevated risk despite full adjustments. When we focused on men and women who reported never smoking, there remained over a 2-fold increased risk of CVD death for high SHS that was minimally affected by adjustment for biological covariates. The excess risk was exactly 2-fold after full adjustment for all risk factors.

Discussion

The aim of the present study was to examine the association between objectively measured SHS and incident CVD death and the extent to which this association could be explained through novel (nonconventional) mechanisms. First, there was an association of SHS exposure with all-cause mortality and CVD death, which confirms results from 2 previous studies (4,5). We observed elevated levels of low-grade inflammation, indexed by CRP, in participants exposed to high SHS, and this partly explained the elevated risk of CVD and all-cause death associated with high SHS in the total cohort but not in the sub-group of never smokers.

Previous studies on the association between SHS exposure and markers of inflammation and hemostasis have produced inconsistent findings. In a Greek population study, participants with a self-reported exposure to SHS on more than 3 days/week demonstrated elevated levels of CRP, fibrinogen, and white blood cell counts (14), and among Japanese women, exposure to SHS outside the home was related to elevated fibrinogen (15). In studies that have employed objective measures of SHS, data from the Third National Health and Nutrition Examination Survey found associations of high SHS with fibrinogen but not CRP and white cell count (3), although the British Regional Heart Study demonstrated positive associations with all of these biomarkers, plus interleukin-6 and von Willebrand factor (1). Previous studies have reported, on the basis of self-reported SHS exposure, modest—typically 1.2- to 1.3-fold—increase in risk of CVD (16). A 1.4-fold increased risk was reported in a study using objective measures (4). Our data with a 1.2-fold excess risk for high SHS and CVD death in the total cohort is largely comparable with these figures, except for the associations in "never-smokers" that is far larger than previous reports. In the case of "never-smokers" there remained a 2-fold increased risk of CVD death for high SHS exposure after full adjustment for psychosocial, behavioral, and biological risk factors. In never smokers the associations of SHS with inflammatory and hemostatic risk factors were nonsignificant (data not shown), which is consistent with previous findings (1). Thus, other mechanisms might be responsible for the excess risk of CVD. For example, experimental data suggests that SHS exposure can elicit acute endothelial dysfunction, although precise mechanisms remain unclear because the effects of SHS on the number and functional activity of

Table 3 Cox Proportional Hazards Models of SHS Exposure, Smoking, and CVD Mortality

Exposure	Event/N	Age-Adjusted	Model 1	Model 2	Model 3	Fully Adjusted
All	364/13,443					
Low SHS	52/1,703	1.00 (Reference)	1.00	1.00	1.00	1.00
Medium SHS	114/5,088	0.89 (0.64–1.23)	0.88 (0.63–1.22)	0.85 (0.61–1.18)	0.88 (0.64–1.23)	0.86 (0.62–1.19)
High SHS	73/2,793	1.21 (0.85–1.73)	1.08 (0.75–1.54)	1.00 (0.69–1.43)	1.11 (0.77–1.58)	0.97 (0.68–1.40)
Smokers	125/3,859	2.44 (1.75–3.40)	2.12 (1.52–2.97)	2.03 (1.45–2.85)	2.04 (1.46–2.86)	1.74 (1.24–2.46)
Log cotinine (/U)		1.21 (1.15–1.25)	1.18 (1.13–1.23)	1.17 (1.12–1.23)	1.16 (1.12–1.22)	1.14 (1.09–1.19)
Never-smokers	96/5,500					
Low SHS	15/1,025	1.00	1.00	1.00	1.00	1.00
Medium SHS	49/3,024	1.28 (0.72–2.28)	1.28 (0.71–2.28)	1.28 (0.71–2.29)	1.35 (0.75–2.42)	1.33 (0.74–2.39)
High SHS	32/1,455	2.22 (1.20–4.12)	2.02 (1.09–3.75)	1.98 (1.05–3.72)	2.22 (1.19–4.15)	2.00 (1.06–3.78)
Log cotinine (/U)		1.72 (1.21–2.44)	1.62 (1.13–2.32)	1.60 (1.11–2.30)	1.69 (1.18–2.42)	1.60 (1.11–2.31)

Values are hazard ratio (95% CI) unless otherwise indicated. All models are mutually exclusive of one another. Model 1 (behavioral), adjusted for age, sex, moderate–vigorous physical activity (none, up to 3/week, >3/week). Model 2 (psychosocial), adjusted for age, sex, social status (I/II professional/intermediate, III skilled nonmanual/manual, IV/V part skilled/unskilled), survey location (England, Scotland), psychological distress (General Health Questionnaire -12 <4 or ≥4). Model 3 (biological), adjusted for age, sex, log C-reactive protein, fibrinogen, HDL-C, systolic blood pressure.
Abbreviations as in Table 2.

Table 4 Cox Proportional Hazards Models of SHS Exposure, Smoking, and All-Cause Mortality

Exposure	Event/N	Age-Adjusted	Model 1	Model 2	Model 3	Fully Adjusted
All	1,221/13,443					
Low SHS	153/1,703	1.00	1.00	1.00	1.00	1.00
Medium SHS	349/5,088	0.89 (0.74–1.08)	0.88 (0.73–1.07)	0.85 (0.70–1.03)	0.89 (0.74–1.08)	0.86 (0.71–1.05)
High SHS	233/2,793	1.25 (1.02–1.53)	1.15 (0.94–1.42)	1.07 (0.87–1.31)	1.15 (0.93–1.41)	1.03 (0.83–1.27)
Smokers	487/3,859	2.89 (2.40–3.48)	2.60 (2.16–3.14)	2.44 (2.02–2.95)	2.52 (2.09–3.04)	2.19 (1.81–2.65)
Log cotinine (/U)		1.23 (1.21–1.26)	1.21 (1.19–1.24)	1.21 (1.18–1.24)	1.21 (1.18–1.21)	1.18 (1.16–1.21)
Never-smokers	273/5,500					
Low SHS	56/1,025	1.00	1.00	1.00	1.00	1.00
Medium SHS	142/3,024	0.97 (0.71–1.32)	0.96 (0.70–1.31)	0.94 (0.69–1.28)	1.00 (0.73–1.36)	0.98 (0.71–1.33)
High SHS	75/1,455	1.33 (0.94–1.88)	1.26 (0.89–1.79)	1.24 (0.87–1.77)	1.31 (0.92–1.86)	1.27 (0.89–1.81)
Log cotinine (/U)		1.26 (0.99–1.60)	1.21 (0.95–1.55)	1.21 (0.95–1.55)	1.24 (0.97–1.58)	1.21 (0.95–1.55)

Values are hazard ratio (95% CI) unless otherwise indicated. All models are mutually exclusive of one another. Model 1 (behavioral), adjusted for age, sex, moderate-vigorous physical activity (none, up to 3/week, >3 /week). Model 2 (psychosocial), adjusted for age, sex, social status (I/II, III, IV/V), survey location (England, Scotland), psychological distress (General Health Questionnaire-12 <4 or ≥4). Model 3 (biological), adjusted for age, sex, log C-reactive protein, fibrinogen, HDL-C, systolic blood pressure.

Abbreviations as in Tables 2 and 3.

circulating endothelial progenitor cells is inconsistent (17,18). This mechanism might account for the association of SHS with circulating markers of endothelial cell activation, such as von Willebrand factor (1). Interestingly, there was no association between SHS exposure and CVD in ex-smokers. This might be partly because ex-smokers already have heightened risk of CVD in comparison with never-smokers, thus SHS exposure might not add to existing risk. Indeed, inflammatory mediators like CRP are still significantly raised in ex-smokers up to 10 to 20 years after quitting (7), suggesting a persistent low-grade inflammatory response in former smokers. Former smokers might also be advised to quit because of existing health problems; thus, the associations might in part also be explained by reverse causation. Our data confirm the strong association between active smoking and CVD/all-cause mortality (19), although the estimated effects were lower when using the objective indicator.

The present data were collected before the introduction of smoke-free legislation in England and Scotland. The smoking ban seems to have already had a considerable impact on the health of the British population (20), although we were unable to estimate the effects of this intervention in these analyses, because follow-up data on cotinine were not available. However, we would not expect that our results have been confounded by the smoking ban, because our study includes only 7 months of CVD deaths after the introduction of the ban (July 2007). We were also unable, due to the lack of follow-up data on cotinine, to account for the effects of changes in smoking behavior that are known to fluctuate over time. There was a large amount of missing data on alcohol intake and body mass index; thus, we were unable to account for these factors in our analyses. However, analyses in a smaller sub-sample of participants with available data on alcohol and body mass index suggested that the association between SHS exposure and CVD was not explained by these variables.

In summary, very few large-scale population-based studies have collected objective biochemical markers of SHS exposure with follow-up data on mortality. Thus, we have presented novel data on the association between objectively measured SHS and incident CVD death in a nationally representative sample of British adults. We observed elevated levels of low-grade inflammation in otherwise healthy participants exposed to high SHS, and this partly explained their elevated risk of CVD death.

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Key Words: cotinine ■ epidemiology ■ inflammation ■ mortality ■ nicotine ■ passive smoke.

APPENDIX

For supplementary tables and Methods, please see the online version of this article.